

Response to the reviewers

Thank you for considering our manuscript. We are very grateful for the reviewers' valuable comments and suggestions, and we have used them to revise and improve our manuscript.

Please watch the revised documents. The amendments are clarified with the track change option of MS Word in the revised ones. Our responses to all of the comments by the reviewers are written below.

We hope that this revision will meet with your approval.

Sincerely yours,

On the behalf of the authors,
Akihiro Shiina MD, PhD
Chiba University Center for Forensic Mental Health

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Criteria Checklist for New Manuscript Peer-Review

2 Abstract. BACKGROUND IS INCOMPLETE: SHOULD MENTION WHY (SUPPORTIVE INFORMATION) BLONANSERIN WAS SELECTED FOR THIS WORK. METHOD IS INCOMPLETE: IT SHOULD CLEARLY STATE THE SIZE OF THE SAMPLE (N = 1), GENDER, RANGE OF AGE OF THE PARTICIPANT. ALSO, AT LEAST FEW LINES ABOUT THE "STUDY PROTOCOL".

Thank you for your comments. We revised the abstract to address the issues you mentioned.

4 Background. Does the manuscript adequately describe the background, present status and significance of the study? YES IT DESCRIBED THEM JUST A COMMENT: THERE ARE YELLOW HIGHLIGHTED NUMBERS (REFERENCES). THE YELLOW SHOULD BE CLEARED.

We addressed this issue.

5 Methods.

THE INCLUSION CRITERIA SHOULD ADD THE LANGUAGE PROFICIENCY OF PARTICIPANTS (EDUCATION OR SCHOLARITY ENOUGH FOR UNDERSTANDING THE INSTRUMENTS, QUESTIONS, SUBJECTS WERE JAPANESE NATIVE SPEAKERS).

We added the description that the participant had to have good Japanese language skills.

THEY MENTION THE SOUTH OAKS GAMBLING SCREEN (SOGS), BUT A REFERENCE SUPPORTING ITS USE SHOULD BE ADDED (NONE INCLUDED). SIMILARLY FOR THE MADRS, YMRS, AND DIEPSS, REFERENCE SUPPORTING THEY USE SHOULD BE ADDED (NONE INCLUDED) IN THE PARAGRAPH DESCRIBING THE DOSE (PAGE 8): 2 TO 12MG/DAY, REFERENCE SUPPORTING THEY USE SHOULD BE ADDED (NONE INCLUDED).

We addressed this issue.

IN THE PARAGRAPH DESCRIBING THE GSAS, PG-YBOCS, BIS-11, the DIEPSS, the MADRS, and the YMRS (PAGE 9): REFERENCE SUPPORTING THEY USE SHOULD BE ADDED (NONE INCLUDED).

We addressed this issue.

6 Results.

IN THE DESCRIPTION OF THE PATIENT, IT IS LISTED THE DIFFERENT MEDICATION SHE IS RECEIVING. THE AUTHORS SHOULD EXPLAIN ABOUT THE ABSENCE OR PRESENCE OF INTERACTIONS BETWEEN THESE DRUGS AND BLONANSERIN (PAGE 10) YES, RESEARCH OBJECTIVES WERE ACHIEVED. THIS STUDY CONTRIBUTION IS TO SHOW THAT BLONANSERIN CAN REDUCE GAMBLING DISORDER PROBLEM, BUT ITS LIMITATION IS EXCESSIVE SALIVATION SIDE EFFECT.

We had examined any of drugs she took, to conclude there was no possibility of interaction between them and blonanserin. We added the description to the revised manuscript.

7 Discussion.

YES, THE DISCUSSION IS FINE BASED ON THE QUESTIONS LISTED. JUST A COMMENT: THERE ARE YELLOW HIGHLIGHTED NUMBERS (REFERENCES). THE

YELLOW SHOULD BE CLEARED.

We addressed this issue.

8 Illustrations and tables.

THE FIGURE NEED TO HAVE A NUMBER (FIGURE 1), DESPITE BEING THE ONLY OF THE MANUSCRIPT.

We addressed this issue.

11 References.

I DETECT OMISSIONS IN DIFFERENT SECTIONS OF THE MANUSCRIPT. THEY WERE DESCRIBED IN THOSE SECTIONS. MOREOVER, REFERENCES ARE NOT SO UPDATED. NEED TO ADD MORE REFERENCES FROM 2015 TO 2020 PERIOD. I CHECK AND FOUND THAT 8 OUT OF 35 REFERENCES (23%) ARE FROM 2015 TO 2019 (NO INCLUSION OF 2020)

We have conducted comprehensive literature search again. After that, we found a latest systematic review of treatment for gambling disorder, to be cited in the introduction section. Also, we found some new studies about blonanserin, but none of them referred to the effect of gambling disorder.

OTHERS COMMENTS:

FUTURE STUDIES SHOULD INCLUDE: LARGER SAMPLES, DOUBLE BLINDED WITH BOTH GENDERS FOR ELIMINATE PLACEBO OR RELATED BIAS AND CONFIRM THE ABSENCE OR EXISTENCE OF GENDER DIFFERENCES OF BLONANSERIN.

1- CAN BE CONFIRMED BLONANSERIN EFFECTIVENESS FOR REDUCING GAMBLING DISORDER IN LARGE SAMPLE AND DOUBLE BLIND STUDIES? 2- ARE POTENTIAL GENDER DIFFERENCES IN BLONANSERIN EFFECTS (THE PARTICIPANT OF THE STUDY WAS FEMALE)? 3- CAN BA BLONANSERIN COMBINED WITH OTHER DRUG (COMBO) FOR REDUCING THE SALIVATION SIDE EFFECT WITHOUT DECREASING THE BENEFIT ON GAMBLING DISORDER?

We added some description regarding the limitation of our study and future perspective.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

1.It is a pity that the participant got mild intellectual disability. Despite the author's explanation, this case does not show the effect of the drug on normal intellectual patients who are the major part. Did the authors enroll and complete only one patient in the trial, which began in 2016? What about the other two patients who didn't complete the experiment? Why was the experiment designed to include three patients?No other eligible patients in 4 years?

Thank you for your concern. This study was conducted during 2016 – 2017. Because of the limited budget, we planned to recruit up to three patients for participation. As a result, only one patient participated (nobody refused to participate or dropped out). After the termination of the trial, we could not gain additional budget to conduct subsequent studies. Therefore, we decided to publish the result as a case report at present. We added the description explaining it in the result section.

2.A blood examination was conducted 2 and 6 weeks after the start of the trial, however the authors do not show any relevant results.

We added the description to the manuscript.

3.In the part of discussion: We conducted a clinical trial to examine the use of blonanserin to treat gambling disorder. The results suggested that blonanserin might be effective in mitigating gambling behaviors but that it may also carry a risk of adverse effects. But in the part of abstract: Conclusion: This case suggests that blonanserin is an effective treatment for patients with gambling disorder who resist standard therapies. Inconsistent conclusions need to be revised.

Thank you for your suggestion. We revised the abstract.

4.The authors should provide an informed consent with the patient's signature.

We attached the informed consent form. However, the Institutional Review Board does not permit the disclosure of the full name or any other type of personal identifiable information of the participants. Therefore, we concealed a part of the document.